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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,454	01/14/2002	Guido Grandi	PP01591.101	4170

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EXAMINER	
MINNIFIELD, NITA M	

ART UNIT	PAPER NUMBER
1645	

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01/27/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/914,454	GRANDI ET AL.	
	Examiner	Art Unit	
	N. M. Minnifield	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,8-21,23,24,32-39 and 43-48* is/are pending in the application.

4a) Of the above claim(s) *32-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 6 8-21 23 24 43-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicants' amendment filed November 2, 2007 is acknowledged and has been entered. Claims 5, 7, 22, 25-31 and 40-42 have been canceled. Claims 12-14 have been amended. New claims 46-48 have been added. Claims 1-4, 6, 8-21, 23, 24 and 43-48 are now pending in the present application. All rejections have been withdrawn in view of Applicants' amendment to the claims and/or comments, with the exception of those discussed below.

2. Claims 1-4, 6, 8-21, 23, 24 and 43-48 have been examined in the instant application.

3. This application contains claims 32-39 have been drawn to an invention nonelected with traverse in the paper filed January 24, 2005. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

4. Claims 1-4, 6, 8-21, 23, 24 and 43-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Claassen et al (Vaccine, 1996, 14/10:1001-1008), Garcon et al (WO 98/56414), in view of Krieg et al (WO 98/18810) and Schwartz et al (WO 98/55495).

Claim 1 is directed to an immunogenic composition comprising: an immunostimulating amount of a Neisseria antigen; and an immunostimulating amount of an adjuvant composition comprising: (i) an oligonucleotide comprising

at least one CG motif; and (ii) an emulsion comprising submicron oil droplets and an emulsifying agent, wherein the ratio of the emulsifying agent to the oil in said emulsion allows production of an emulsion wherein at least 80% of said oil droplets are less than 1 micron in diameter.

Claassen et al teaches a composition comprising a *Neisseria meningitidis* antigen, proteins from *Neisseria meningitidis* serogroup b, and an adjuvant (abstract; materials and methods, p. 1002). Claassen et al teaches the use of aluminum phosphate as the adjuvant.

Garcon et al teaches that oil in water emulsions having an oil droplet diameter of substantially 300-600 nm diameters in size (i.e. less that 1 micron in diameter) and that they can be used as vaccine adjuvants (abstract; p. 4; claims). The adjuvants comprise metabolisable oil squalene (i.e. a terpenoid), alpha-tocopherol and TWEEN80 (p. 1). Garcon et al teaches that the emulsion may be used own its own or with other adjuvants or immunostimulants (p. 4). Garcon et al teaches the use of polyoxyethylene sorbitan monooleate (TWEEN 80), an emulsifying agent (p. 5). Garcon et al teaches that the vaccine formulation can contain an antigen and that the antigen can be derived from bacterial pathogens such as *Neisseria spp*., including *N. gonorrhea* and *N. meningitidis* (for example capsular polysaccharides and conjugates thereof, transferring-binding proteins, lactoferrin binding proteins, PilC, adhesions) (see p. 5). Garcon et al teaches that the composition comprise 2 to 10% squalene (i.e. 0.5 to 20% oil) and 0.3 to 3% TWEEN80, the emulsifying agent (i.e. 0.01 to 0.5% emulsifying agent) (see p. 10). Claassen et al and Garcon et al teach the claimed invention except for the adjuvant composition comprising an oligonucleotide comprising at least on CG motif.

However, Krieg et al teaches that CpG oligonucleotides are immunostimulatory and are useful as synthetic adjuvants (abstract; p. 1; claims). Krieg et al teaches that the oligonucleotides can be used to treat, prevent or ameliorate disorders that include bacterial infection (p. 10). The infectious bacteria include *Neisseria gonorrhoeae* and *Neisseria meningitidis* (p. 17). The prior art teaches that the oligonucleotide can have a phosphorothioate bond (p. 22). "Nonspecific simulators of the immune response are known as adjuvants. The use of adjuvants is essential to induce a strong antibody response to soluble antigens (reference omitted). The overall effect of adjuvants is dramatic and their importance cannot be overemphasized. The action of an adjuvant allows much smaller doses of antigen to be used and generates antibody responses that are more persistent. The nonspecific activation of the immune response often can spell the difference between success and failure in obtaining an immune response. Adjuvants should be used for first injections unless there is some very specific reason to avoid this." (p. 33, l. 30-38) Krieg et al teach the claimed SEQ ID NO: 1. "Recently an intense drive to find potent adjuvants with more acceptable side effects has led to the production of new synthetic adjuvants. The present invention provides the sequence 1826 TCCATGACGTTCCTGACGTT (SEQ ID NO: 10), which is an adjuvant including CpG containing nucleic acids. The sequence is a strong immune activating sequence and is a superb adjuvant, with efficacy comparable or superior to complete Freund's, but without apparent toxicity." (p. 34, l. 15-20) Krieg et al teaches the use of additional adjuvants in the composition. "Immunostimulatory oligonucleotides and unmethylated CpG containing vaccines, which directly activate lymphocytes and co-stimulate an antigen-specific response, are fundamentally different from conventional adjuvants (e.g. aluminum

precipitates), which are inert when injected alone and are thought to work through absorbing the antigen and thereby presenting it more effectively to immune cells. Further, conventional adjuvants only work for certain antigens, only induce an antibody (humoral) immune response (Th2), and are very poor at inducing cellular immune responses (Th1). For many pathogens, the humoral response contributes little to protection, and can even be detrimental." (p. 65, l. 1-8)

Schwartz et al teaches a composition comprising an immunostimulatory oligonucleotide (CpG) and antigen (abstract). Schwartz et al teaches that the antigen can be protein, glycoproteins, polysaccharides and lipids (p. 4, l. 33-34; p. 12, l. 9-28; pp. 12-13). "In another embodiment, the immunomodulatory composition comprises an oligonucleotide that contains at least one immuno-stimulatory (ISS) octanucleotide and a facilitator selected from the group consisting of co-stimulatory molecules, cytokines, chemokines, targeting protein ligand, a trans-activating factor, a peptide, and a peptide comprising a modified amino acid." (p. 4, l. 36-39; p. 12, l. 9-28) Schwartz et al teaches that the composition can also comprise the oligonucleotide, an antigen and an adjuvant (p. 5, l. 1-2; p. 8, l. 19-23). The adjuvants include alum, lipid emulsions and polylactide/polyglycolide microparticles as well as oil-in-water emulsions, mycobacterium cell wall preparations and muramyl peptide (p. 12; pp. 15-19; claims). Schwartz et al teaches that the compositions provide for methods of treating subjects in need of immune modulation; the subjects may be suffering from infectious diseases and bacterial infections (p. 5; claims). Schwartz et al teaches that the CG motif be flanked by two purines immediately 5' to said motif and two pyrimidines immediately 3' to said motif (p. 7, l. 14-21). Schwartz et al teaches that an immunomodulatory facilitators, molecules which support and/or

enhance the immunomodulatory activity of an oligonucleotide, can be used in the composition, which include cytokines and/or adjuvants (p. 14, l. 15-36), as well as compositions comprising an oligonucleotide, antigen and adjuvant (claims).

In view of the combined teachings of Claassen et al, Garcon et al, Krieg et al and Schwartz et al it would have been obvious to a person of ordinary skill in the art to prepare a composition that comprises a Neisseria antigen, CG oligonucleotide and emulsion and optionally another adjuvant. The prior art teaches that the Neisseria antigen can be *Neisseria meningitidis, Neisseria gonorrhoeae* an antigen from *Neisseria meningitidis* serogroup B (Claassen et al and Garcon et al). An adjuvant composition comprising an oligonucleotide comprising at least one CG motif and an emulsion are taught in Kreig et al, Schwartz et al and Garcon et al. Krieg et al teaches the claimed oligonucleotide as set forth in SEQ ID NO: 1 and teaches that it is a strong immune activating sequence and is a superb adjuvant. Krieg et al, Schwartz et al and Garcon et al teach the use of multiple adjuvants and/or immunostimulants in the compositions. Schwartz et al teaches that the specifically claimed additional adjuvants can be used in the compositions to enhance the immunomodulatory activity. The claimed invention is prima facie obvious in view of the combination of teachings as a whole found in Claassen et al, Garcon et al, Krieg et al and Schwartz et al, absent any convincing evidence to the contrary.

The rejection is maintained for the reasons of record. Applicant's arguments filed November 2, 2007 have been fully considered but they are not persuasive. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which

applicant relies (i.e., synergistic immunogenicity, immunogenic response greater than the sum of the response to the antigen with each adjuvant individually, increased immunogenicity approximately five fold after the first dose and seven fold after the second dose..., etc) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants have asserted that Krieg et al fails to provide any teaching that would guide one of skill in the art to select *Neisseria* rather than any of the at least one hundred other pathogenic organisms described in the specification and that the claimed invention is nonobvious. However, it is noted that Kreig et al is not relied upon, specifically or solely, for the teaching of a composition comprising *Neisseria* antigen, but for its teaching of using the CpG oligonucleotide as an adjuvant, immunostimulant or immunostimulating agent in a composition that does comprise other or additional antigens. Claassen et al and Garcon et al are relied upon to teach a composition comprising a *Neisseria* agent. Applicants have asserted that Schwartz et al does not teach the necessity of using a co-stimulatory molecule or even the desirability of such, much less the desirability of oil-in-water over the 28 other choices presented and that at best Schwartz et al only suggests that it would be obvious to try combining one of twenty-nine different costimulatory molecule

with and ISS. Applicants have asserted that the same is true for Garcon et al (that Garcon et al adds to the number of antigens possible for the immunogenic or vaccine composition). In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

With regard to a reasonable expectation of success, it is noted that Applicants have not specifically claimed that the composition has synergistic immunogenicity.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Claassen et al teaches a composition comprising a *Neisseria meningitidis* antigen, proteins from *Neisseria meningitidis* serogroup b, and an adjuvant (abstract; materials and methods, p. 1002). Claassen et al teaches the use of aluminum phosphate as the adjuvant.

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Adjuvants should be used for first injections unless there is some very specific reason to avoid this." (p. 33, l. 30-38) Krieg et al teach the claimed SEQ ID NO: 1. "Recently an intense drive to find potent adjuvants with more acceptable side effects has led to the production of new synthetic adjuvants. The present invention provides the sequence 1826 TCCATGACGTTCCTGACGTT (SEQ ID NO: 10), which is an adjuvant including CpG containing nucleic acids. The sequence is a strong immune activating sequence and is a superb adjuvant, with efficacy comparable or superior to complete Freund's, but without apparent toxicity." (p. 34, l. 15-20) Krieg et al teaches the use of additional adjuvants in the composition. "Immunostimulatory oligonucleotides and unmethylated CpG containing vaccines, which directly activate lymphocytes and co-stimulate an antigen-specific response, are fundamentally different from conventional adjuvants (e.g. aluminum precipitates), which are inert when injected alone and are thought to work through absorbing the antigen and thereby presenting it more effectively to immune cells. Further, conventional adjuvants only work for certain antigens, only induce an antibody (humoral) immune response (Th2), and are very poor at inducing cellular immune responses (Th1). For many pathogens, the humoral response contributes little to protection, and can even be detrimental." (p. 65, l. 1-8)

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ligand, a trans-activating factor, a peptide, and a peptide comprising a modified amino acid." (p. 4, l. 36-39; p. 12, l. 9-28) Schwartz et al teaches that the composition can also comprise the oligonucleotide, an antigen and an adjuvant (p. 5, l. 1-2; p. 8, l. 19-23). The adjuvants include alum, lipid emulsions and polylactide/polyglycolide microparticles as well as oil-in-water emulsions, mycobacterium cell wall preparations and muramyl peptide (p. 12; pp. 15-19; claims). Schwartz et al teaches that the compositions provide for methods of treating subjects in need of immune modulation; the subjects may be suffering from infectious diseases and bacterial infections (p. 5; claims). Schwartz et al teaches that the CG motif be flanked by two purines immediately 5' to said motif and two pyrimidines immediately 3' to said motif (p. 7, l. 14-21). Schwartz et al teaches that an immunomodulatory facilitators, molecules which support and/or enhance the immunomodulatory activity of an oligonucleotide, can be used in the composition, which include cytokines and/or adjuvants (p. 14, l. 15-36), as well as compositions comprising an oligonucleotide, antigen and adjuvant (claims).

In view of the combined teachings of Claassen et al, Garcon et al, Krieg et al and Schwartz et al it would have been obvious to a person of ordinary skill in the art to prepare a composition that comprises a Neisseria antigen, CG oligonucleotide and emulsion and optionally another adjuvant. The prior art teaches that the Neisseria antigen can be *Neisseria meningitidis, Neisseria gonorrhoeae* an antigen from *Neisseria meningitidis* serogroup B (Claassen et al and Garcon et al). An adjuvant composition comprising an oligonucleotide comprising at least one CG motif and an emulsion are taught in Kreig et al, Schwartz et al and Garcon et al. Krieg et al teaches the claimed oligonucleotide as set forth in SEQ ID NO: 1 and teaches that it is a strong immune activating

sequence and is a superb adjuvant. Krieg et al, Schwartz et al and Garcon et al teach the use of multiple adjuvants and/or immunostimulants in the compositions. Schwartz et al teaches that the specifically claimed additional adjuvants can be used in the compositions to enhance the immunomodulatory activity. The claimed invention is prima facie obvious in view of the combination of teachings as a whole found in Claassen et al, Garcon et al, Krieg et al and Schwartz et al, absent any convincing evidence to the contrary.

With regard to Applicants assertion of unexpected results, none of these ELISA titers, potencies or bactericidal activities have been recited in the claims.

Additionally, *KSR International Co. v. Teleflex Inc*., 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one method , and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc*., 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". It well known in the art to use Neisseria antigens and adjuvants in immunogenic compositions or vaccine compositions as shown by Claassen et al or Garcon et al. Garcon et al recognizes that multiple adjuvants can be used in a composition. And Krieg et al and Schwartz et al teach that CpG is an immunostimulatory agent (i.e. adjuvant). Thus, it would be obvious to apply a known technique to a known product to be used in a known method that is ready for improvement to yield predictable results. Thus, the combination of prior art references as combined provided a *prima facie* case of obviousness.

5. No claims are allowed.

6. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert B. Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/N. M. Minnifield/
Primary Examiner, Art Unit 1645
January 21, 2009